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Management of Diabetes Mellitus

JAMES M. MOSS

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Disease-a-Month Series

MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

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Management of Diabetes Mellitus

JAMES M. MOSS

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BECAUSE diabetes mellitus is a chronic disease for which there is no permanent cure, the physician must satisfy himself with measures designed to help the patient live a comfortable normal life for as many years as possible. The best methods of treating one patient are not always the best methods for treating another. It has been demonstrated that those patients who avoid ketonuria, constant glycosuria, or severe hypoglycemic attacks have a lower incidence of the degenerative complications of diabetes and that these complications occur at a later date (31, 21, 52). It is, therefore, desirable that the best possible degree of diabetic control be maintained in each patient and that the treatment be planned to fit the particular needs of that individual. Frustration is the result when the physician tries to fit each patient into a fixed pattern of treatment which he believes is the only proper method. Some authorities recommend strict chemical control of the blood sugar and the maintenance of a sugar-free urine (29), while others are satisfied with control of the symptoms of diabetes and avoidance of ketonuria (60, 6). The criteria of control that are used by the Diabetic Clinic at Georgetown University Hospital are shown in Table 1. These

criteria are sufficiently flexible so that they can be used generally.

TABLE 1.—CRITERIA OF GOOD DIABETIC CONTROL

1. Absence of diabetic symptoms
2. Freedom from hypoglycemic reactions
3. Maintenance of optimum body weight
4. Blood sugar 100–150 mg./100 ml. before each meal
5. Little or no sugar in the urine

CRITERIA OF CONTROL

Control of the symptoms is the first obligation of the physician. No patient who has polydipsia and polyuria can be considered to be well treated. Nocturia may be the only symptom of hyperglycemia and glycosuria. Nocturia should not be readily accepted as part of the normal aging process until it is determined that hyperglycemia does not exist before breakfast or at bedtime. Specific questioning is often necessary to bring out these nondisabling symptoms (60). Weakness and fatigue are classic but vague symptoms. Because of their gradual onset, these may be recognized in retrospect when the patient is feeling better after successful treatment. Myopia often follows hyperglycemia. When the blood sugar falls, hyperopia may occur. If the patient was originally hyperopic, he may have improved vision with an elevated blood sugar and decreased vision with a normal blood sugar (18). Because the symptoms of hyperglycemia are so mild and so variable, chemical tests are needed for the more precise evaluation of diabetic control.

Hypoglycemia is an ever present hazard in patients who are taking insulin, but it is rarely a problem in patients treated with the sulfonylurea drugs (45). Hypoglycemic reactions are embarrassing to the patient and may make it dangerous for him to perform jobs that require constant undivided attention to his duties. Mild hypoglycemic episodes may cause emotional instability or decreased intellectual ability at a critical time for students and businessmen. If the hypoglycemic reaction is severe, the convulsions or loss of consciousness may cause considerable anxiety on the part of relatives and friends. Irreversible brain damage leading to mental deterioration and/or epilepsy (10) may follow prolonged severe reactions. Every large diabetic clinic has

patients who show the residual effects of previous excessive doses of insulin.

During an episode of hypoglycemia the homeostatic mechanisms of the body function in an effort to restore the blood sugar to normal and to keep it elevated. The first response is the secretion of epinephrine by the adrenal medulla (58). This causes the classic symptoms of sweating, pallor, vasoconstriction, palpitation, increased pulse pressure, dilated pupils, nervousness, anxiety, tremor, and hunger. Because it increases the rate of glycogen breakdown in the liver, epinephrine is often effective in raising the blood sugar and preventing the hypoglycemia from progressing to the point of loss of consciousness. This mechanism is ineffective in the malnourished patient who has insufficient glycogen reserves in the liver. The stress of hypoglycemia results in the stimulation of the adrenal cortex to secrete more cortisone, with the result that gluconeogenesis is increased and the blood sugar slowly rises to a higher level (11).

An episode of hypoglycemia sufficiently severe to stimulate this chain of compensatory reactions may be so mild that the patient is unable to recognize it. The physician often needs to perform blood sugar tests before each meal, at bedtime, and sometimes during the night, if he is to diagnose some of these mild transient hypoglycemia episodes (27). When the blood sugar falls slowly, there may be no symptoms of stimulation of the adrenal medulla but only symptoms of depression of the central nervous system. These symptoms of headache, inco-ordination, emotional disturbances, mental confusion, fatigue, drowsiness, and retarded reactions are easily overlooked. The fasting blood sugar may be well over 200 mg./100 ml. in patients who have had a reaction while they were asleep during the night. Without careful study the physician might increase the insulin dose in a patient with such an elevated blood sugar (53). This would result in a more severe nocturnal reaction and a higher fasting blood sugar the next day. Eventually, the insulin dose is increased to the point that the homeostatic mechanisms of the body are overpowered and a temporary normal fasting blood sugar is obtained. By this time the patient is taking a very large dose of insulin and is having almost constant glycosuria with frequent unpredictable and severe hypoglycemic reactions. This is one of the important factors in the etiology of "brittle diabetes" with large insulin requirements (20). When the insulin dose is reduced, these patients

will have less glycosuria and no reactions. Some of the beneficial results of phenformin (see p. 26) and tolbutamide in these patients is probably due to the reduced insulin dose. The avoidance of hypoglycemia seems like an obvious requirement for satisfactory diabetic control, but its occurrence is entirely too frequent in many patients.

The diabetic patient should maintain a body weight that is slightly less than the optimum amount shown in the usual height and weight charts (29). Even though the blood sugar may be normal, the patient who is obese cannot be considered to be well controlled. Most obese patients need no medication but need to reduce their caloric intake (26). Because so many of them find it impossible to continue the dietary restrictions, the physician is frequently pressured into prescribing either insulin or oral medication in an effort to attain a normal blood sugar and to relieve the symptoms of the disease. At the other extreme is the thin patient who starves himself to the point of weakness and fatigue in an effort to have a negative urine test. This patient is also poorly controlled. He would be better off on an adequate diet plus hypoglycemic medication. It is important for children to grow at the normal rate. If the diet is inadequate in calories, the blood sugar may be normal but the child will show statural retardation and delayed sexual development (32).

Ideally the blood sugar should be within the normal range throughout the entire 24 hours. From a practical standpoint, we test the blood sugar before each meal and aim to keep it between 90 and 130 mg./100 ml. if the Somogi-Nelson (57, 49) blood sugar method is used, or between 110 and 150 mg./100 ml. if the Folin-Wu method is used (17). If there are any hypoglycemic reactions, regardless of how mild, the insulin dose must be reduced and the average blood sugar allowed to rise. If the high and low points in the blood sugar curve follow a pattern, it is usually possible to smooth this out by a minor rearrangement of the diet. For example, the patient with a fasting blood sugar of 180 mg./100 ml. and an afternoon blood sugar of 90 mg./100 ml. may become perfectly controlled if the bedtime snack is added to the lunch. If dietary rearrangement is inadequate, it may become necessary to use a different type of insulin or to give a divided dose of the same insulin. In older patients with severe arteriosclerosis, a higher blood level is permitted at all times (48).

The complete absence of glycosuria is the least important

of the five criteria of control listed in Table 1; yet many patients and physicians consider it to be of supreme importance. It is well for all patients to have a negative urine, but not at the expense of hypoglycemia or an inadequate diet. In children there is a rapid rise in the blood sugar immediately after meals and also a relatively low renal threshold for glucose. The blood sugar may be high after meals but then drop to a reasonable level before the next meal. If the bladder was emptied and the urine tested for sugar only before each meal and at bedtime, it is possible that all specimens will contain sugar. If the patient empties his bladder 3 or 4 hours after a meal and then tests a urine specimen ½ hour later, it is likely that this urine will be negative. Because of the difficulty in obtaining a urine specimen in children, it is usually necessary to test whatever specimen is on hand. Many juvenile diabetics have unnecessary insulin reactions because of futile attempts to avoid postprandial glycosuria. The other extreme is seen in elderly patients who have a high renal threshold. It is not unusual for these patients to have a blood sugar value which varies between 200 and 300 mg./100 ml. and yet the patient and the physician are well satisfied with the control because the urine is sugar free. Recent studies with fat tolerance tests show that the serum lipids rise to a higher level and remain elevated longer when the blood sugar is elevated (23). Thus it would appear that the mean blood sugar level is an important factor in determining the rate of development of arteriosclerosis in patients with diabetes. The amount of sugar utilized and the height of the blood sugar level are more important to the health of the patient than is the amount of sugar lost in the urine. Twenty-four-hour quantitative urine sugar determinations were discontinued at Georgetown 10 years ago. It is unlikely that we are missing any information that could not be obtained more easily and more accurately by other means.

The avoidance of ketonuria (60) is not listed as one of the criteria of good diabetic control, because it will occur automatically when the other criteria are satisfied. Some ketonuria may occur in patients in good diabetic control, but who are purposely losing weight because of a low-calorie diet. Most patients with ketosis will have the classic symptoms plus headache, nausea, anorexia, malaise, drowsiness, and muscle cramps. These symptoms should alert both the patient and the physician to the possibility of impending trouble. Acidosis can come on much more rapidly in children than in adults.

Therefore, the urine should be tested for ketones at frequent intervals, and especially whenever the child feels sick or has repeated heavy glycosuria (11). A new stick test for both acetone and sugar is in the process of clinical trial. This makes it very easy for the patient to test for both in 15 seconds. This test should become a routine procedure four times each day in children.

All of the above criteria must be satisfied if the physician is to give his patient the best possible treatment. Such satisfactory control can be obtained in about three fourths of the private patients but in only one fourth of the clinic patients. This is due partly to the fact that the clinic patient cannot afford to eat as well as he would like to. He sometimes has to eat whatever is available, and often he eats as much as is available at that time. A more important factor is the difference in the intelligence and motivation of the clinic and private diabetic patient. Those physicians whose experience is limited to clinic patients may sometimes become frustrated to the point that they believe that good diabetic control is an impossible goal in any patient.

DIABETES DETECTION AND DIAGNOSIS

The longer the duration of poorly controlled diabetes, the greater is the incidence of degenerative complications. Unrecognized diabetes, even though mild, is obviously uncontrolled until it becomes severe enough to be recognized. By this time the patient often has developed irreversible degenerative complications (43). For every diabetic patient under treatment in the United States there is another undiagnosed diabetic who needs treatment (64). The early detection of these unrecognized diabetics and the prompt institution of good control is one important step in the prevention of disability due to diabetes. A survey of the presenting complaints of diabetic patients (43) showed that only one third of them had complaints that were recognized as being typical of diabetes. Another third had complaints that were due to diabetes or its complications but which were unusual. In the latter patients the physician failed to think of diabetes until glycosuria was found by the performance of a routine urinalysis. The complaints in this group included the following: pruritus vulvae, blurred vision, muscle pains, indigestion, constipation, hemorrhoids, amenorrhea, myocardial infarction, pyogenic infections, postural hypotension, gangrene, and

complications of pregnancy. The other third of the patients had no complaints and were found to have glycosuria or hyperglycemia at the time of a routine screening test done as part of diabetes detection drive or of an insurance, preemployment, hospital admission, or annual physical examination. In detection drives, glycosuria is found in 0.2 to 1.7% of all the people tested (5). If the group is limited to relatives of diabetics, people over age 40 years, or people who are

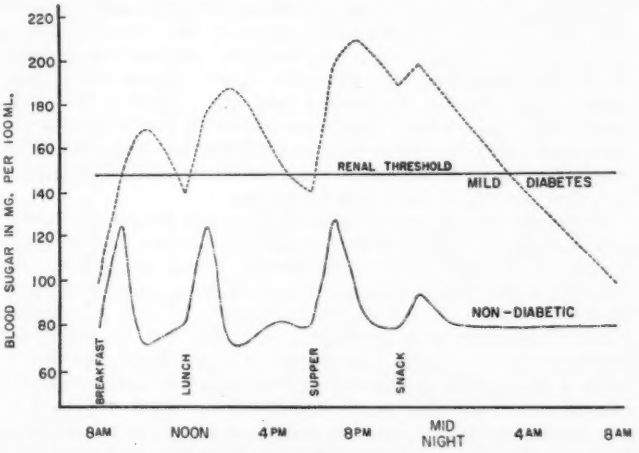

FIG. 1.—Range of blood sugar through the day in a patient with mild diabetes and in a nondiabetic person, each eating three meals and a snack each day.

overweight, the number of positives rises to as high as 4%. In patients with a high renal threshold or with very mild diabetes, the diagnosis may be missed on routine urinalysis but picked up by the performance of a postprandial blood sugar test (5).

For screening purposes it is desirable that the urine or blood specimen be collected 2 hours after a meal containing a large amount of carbohydrate. As shown in Figure 1, patients with mild diabetes have a normal fasting blood sugar and a negative fasting urine test but have hyperglycemia and glycosuria after large meals (64). The occurrence of glyco-

suria is presumptive evidence for diabetes until it is proved to be due to some other cause. Glycosuria in a pregnant woman may be due to the low renal threshold of pregnancy, and in a lactating woman it may be due to lactosuria. However, it is never safe to make either of these diagnoses until after a glucose tolerance test has been done to rule out the possibility of diabetes. Accurate blood sugar tests are needed for the definitive diagnosis of diabetes, and no diagnosis should be based on the results of only one blood sugar test. If the true blood sugar is over 110 mg./100 ml. fasting; over 150 mg./100 ml. at any time; or over 120 mg./100 ml. 2 hours after a meal, it is likely that the patient has diabetes (1). (The standards for Folin-Wu blood sugars are 20 mg. higher.) The higher the blood sugar, the greater is the likelihood that the patient does have diabetes mellitus and the lesser the need for other tests to confirm the diagnosis. With borderline blood sugar tests, more extensive testing is needed in order to make an accurate diagnosis.

A glucose tolerance test is needed for the proper evaluation of the diabetes suspect who has mild symptoms and who has a normal or slightly elevated fasting blood sugar test (see Fig. 2). A decreased glucose tolerance may result from starvation, infection, fever, emotional stress, or lack of exercise (28). Therefore, it is important that the test be done in a patient who has been fed a high carbohydrate diet for at least 3 days prior to the test and who is not acutely ill. The standard test consists of a fasting blood sugar followed by the oral ingestion of 100 Gm. of glucose in 500 ml. of water flavored with lemon juice. Blood specimens are drawn at 1 and 2 hours after the ingestion of the glucose. Sometimes the sensitivity of the test is improved by also drawing a specimen at ½ and 3 hours after the ingestion of the glucose. Prolonging the test beyond 3 hours is of no value in the diagnosis of diabetes but is done when the possibility of spontaneous hypoglycemia is suspected. There is no point in doing a glucose tolerance test when the true fasting blood sugar is elevated over 130 mg./100 ml., since this level is diagnostic of diabetes. The glucose tolerance test gives no guide as to the severity of the diabetes, the response to tolbutamide, or the need for insulin (29). The most critical value for the detection of mild diabetes is the height of the blood sugar drawn 2 hours after the glucose. Normally this has returned to the fasting level, but in patients with diabetes this is higher than 120 mg./100 ml. (47).

In the past year the tolbutamide response test has been reported to aid in the evaluation of the mild patient who has a borderline glucose tolerance test. This test is based on the fact that normal people respond better to the intravenous administration of 1 Gm. of sodium tolbutamide than do patients with mild diabetes (62). A blood specimen is drawn

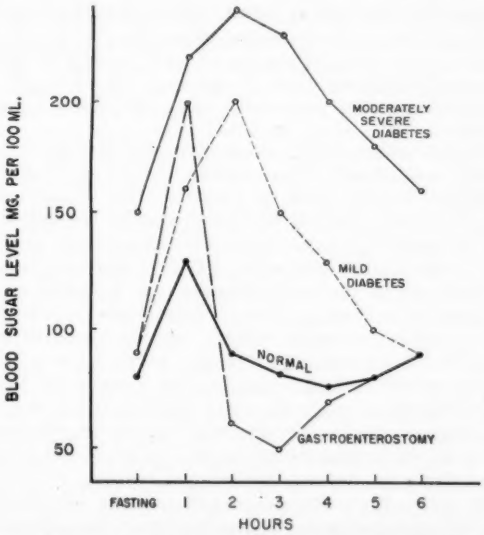

FIG. 2.—Glucose tolerance curves seen in the nondiabetic, the mild diabetic, the moderate diabetic and in the patient with alimentary hyperglycemia, after 100 Gm. of glucose orally.

before the administration of the tolbutamide and again 20 and 30 minutes later. In the diabetic the fall in the blood sugar is less than 20%, and in the nondiabetic the fall is greater than 20%. The exact standard for this test will be defined after further use. This test leads to a more accurate diagnosis in the borderline patient.

Recognition of the prediabetic is more difficult, since these patients have both a normal glucose tolerance and a normal tolbutamide response test. Under stress, these are the patients who develop a decreased glucose tolerance and eventually

clinical diabetes. Fajans and Conn (16) have introduced a measured stress that can be reproduced to sharply delineate this group. They give 50 mg. of Hydrocortone by mouth 8½ and again 2 hours before the glucose tolerance test is repeated. There was no effect in 97% of the patients, while 3% showed impaired glucose tolerance. Of those with a family history of diabetes, 24% showed impaired tolerance on this test. Follow-up studies have shown that clinical diabetes most often occurred in the patients with the impaired glucose tolerance under stress. Perhaps diabetes could be postponed if prediabetic patients were recognized early enough to start prophylactic weight reduction and, possibly, tolbutamide treatment.

Renal glycosuria is due to decreased tubular reabsorption of glucose associated with a normal blood sugar and a normal glomerular filtration of glucose (9). The condition is diagnosed by the finding of glycosuria in a patient with a normal glucose tolerance test. This metabolic abnormality has an incidence of less than 1/1,000 and is easily recognized if all positive urine sugar tests are followed up by adequate blood sugar testing. Some of the patients who have not had adequate blood sugar testing receive an incorrect diagnosis of diabetes mellitus and are started on a course of insulin in a futile effort to control the glycosuria. More commonly, patients actually do have mild diabetes mellitus but are misdiagnosed as having renal glycosuria because they have a normal fasting blood sugar. In pregnancy there is a normal fall in the fasting blood sugar level of about 10 mg./100 ml. (38). With the decreased tubular reabsorption for glucose which occurs in pregnancy, it is not uncommon to have marked glycosuria associated with a normal fasting blood sugar (54). This makes it very difficult to recognize the latent diabetic tendency that may be brought to the surface by the pregnancy. It is important that diabetes be excluded by a glucose tolerance test before the pregnant woman is given an incorrect diagnosis of renal glycosuria (38).

DIABETIC DIETS

Regardless of which drugs are used in the treatment of diabetes, it is essential that the patient adhere to some form of dietary restriction. Even the physicians who advocate a free diet (60) advise their patients to avoid concentrated

sources of carbohydrates and to avoid obesity. There is uniform agreement that the diet should be as much like the average American diet as possible (42). For many persons, no modification of their current eating habits is necessary after the diagnosis of diabetes is made. A consideration of the reasons for the dietary restrictions will help the physician use better judgment in his prescription (12).

The provision of enough calories for the maintenance of an optimal body weight while the patient carries out his usual activities is the first consideration. The obese patient needs a low calorie diet so that he will burn his own fat and reduce his weight to the optimal level. The malnourished patient needs to be given extra calories in order to gain weight. The child must be provided with sufficient calories to permit normal growth. The patient taking insulin must have a constant caloric intake each day. If he is given enough insulin for a 2,000-calorie diet but eats 3,000 calories, he will have hyperglycemia; but if he eats 1,000 calories, it is obvious that he will have an insulin reaction. The diet needs to be constant as to the amount, type of food, and the time of the meals. Most patients do better if they are given a list showing the foods they may have at each meal than if they are given a list of those which they cannot have.

The average 124-pound housewife needs a basic diet of 1,800 calories, while her 150-pound husband with an office job needs 2,200 calories. If the husband is engaged in strenuous physical exertion, his caloric requirement may rise to as high as 3,600 calories. With the laborsaving machinery of today, there are very few people who need so many calories. The elderly patient needs to reduce his daily intake by 300–400 calories if he is to avoid obesity. If the daily caloric intake is 1,000 calories less than the basic requirement, the patient will lose about 2 pounds per week (12). Obese patients are usually given diets of 900–1,500 calories, depending upon their height, age, and physical exertion. From a psychologic standpoint, it is better to start a patient on a low calorie diet and to increase this later on than it is to reduce the caloric intake of an established dietary routine.

The caloric requirements of children vary with their age and with the amount of exercise that they take. The initial diet may be calculated on the basis of 1,000 calories plus 100 calories for each year of age up to age 12 in girls and age 16 in boys. Thus, a 6-year old child would be given 1,600 calories and a 10-year old child 2,000 calories. If the child

is obese, the calories are reduced; but if the child is thin, growing slowly, or constantly hungry, the diet is increased. A hungry child cannot be expected to adhere to a strict diet and cannot be blamed for dietary indiscretions that are due to his effort to receive adequate calories. The caloric intake of children must be increased a little each year. Usually this is best done at the beginning of the summer vacation with a continuation of the same amount of insulin. After school starts in the fall, it is often necessary to increase the insulin dose. In increasing the diet an effort is made to add the extra food prior to the time of the lowest blood or urine sugar tests.

The patient taking insulin must have sufficient carbohydrate available at the time that the insulin is most active. Those patients who take three doses of regular insulin do well on three equal meals each day. If protamine zinc insulin is used, it is essential that the bulk of the calories be provided at the latter part of the day and that the breakfast be relatively small. Thus, the meals might be divided: 20% at breakfast, 30% at lunch, 40% at supper, and 10% at bedtime. With the faster-acting isophane (NPH), lente, or globin insulin, the bedtime feeding can usually be omitted and this food added to the lunch or given in the form of a mid-afternoon snack. A bedtime feeding is essential in all hospitalized patients because the late breakfast and early supper makes them prone to have a nocturnal reaction on almost any type of insulin. After the patient has returned to his usual occupation and most of the blood and urine sugar tests are near normal, minor changes in the diet may be made to lower the high points and raise the low points in the blood sugar curve.

The amount of protein in a diabetic diet should be 1 Gm./kg. of body weight for an adult and two or three times this amount for a child or pregnant woman. The usual tendency is to give more than this basic amount to all. The fluctuations in the blood sugar are less marked on a high protein diet than they are on a high carbohydrate diet. Patients on a high protein diet are less subject to vitamin deficiencies, pyogenic infections, and the stress of a prolonged period of poor diabetic control than are those on a low protein diet. The biggest deterrent to high protein diets is the excessive cost and the difficulty involved in procuring such a diet in restaurants.

Fat is used in the diet to provide extra calories after adequate amounts of protein and carbohydrate have been pro-

vided. A diet that is very low in fat is difficult to prepare, impossible to obtain in a restaurant, and lacking in palatability. The excessively high fat diets of the past had the same disadvantages. A medium fat diet is readily available to all patients and is the one most commonly used today. There is evidence that less arteriosclerosis develops in patients on a low fat diet than in those on a high fat diet (50). There also seems to be some virtue in using unsaturated vegetable fats in preference to the saturated animal fats (2). Until these data have been more thoroughly digested, it seems wise to avoid any drastic changes in the treatment that has been so successful in the past.

The average American diet today derives 40% of its calories from carbohydrate, 40% from fat, and 20% from protein (each gram of carbohydrate and protein yields 4 calories, but each gram of fat yields 9 calories). This gives a 2:1 ratio between the number of grams of carbohydrate and fat instead of a 1:2 ratio of the past generation. Today, some physicians are using a 3:1 or 4:1 ratio in an effort to reduce arteriosclerosis (33). These high carbohydrate diets often cause wide fluctuations in the blood sugar level, so that it becomes necessary to give the patient as many as seven feedings each day. One advantage of the high carbohydrate diets is that the patient is allowed to use some of the concentrated sources of sugar that are usually denied him. This makes it easier for him to eat away from home and not appear to be abnormal. The muscle cells cannot tell the difference between a molecule of glucose derived from cane sugar and a molecule derived from orange juice. Raising the carbohydrate intake high enough to permit a few concentrated sweets often results in better patient co-operation and better control in the long run.

In the past, diabetic diets were made needlessly complicated by the use of the metric system for measurement. Patients who had no conception of a gram were told that they could have 100 Gm. of a 6% vegetable or 200 Gm. of a 3% vegetable. Such diets were successful in diabetic centers, such as the New England Deaconess Hospital, where there were organized classes in instruction (29). For patients who did not have these benefits, these diets were a hopeless mass of confusion. Consequently, the patients usually continued to eat as before. Ten years ago this situation was helped by the publication of a system of food exchanges worked out by a joint committee of the American Diabetic and the Ameri-

can Dietetic Associations. In this system, all foods are classified into one of seven basic groups, depending on the proportion of carbohydrate, protein, and fat. Household measures are used, so that the patient can approximate the proper amount of each food. Because of the great variability in the composition of foods, the use of the weighed system gave the patient an unjustified sense of accuracy. For example: the carbohydrate content of string beans may vary from 3% to 6%, depending on the age when they were picked and the condition of the soil; peas may vary from 7% to 13% under similar circumstances; milk may vary from 3% fat to 6% fat, depending on the breed of the cow. The propor-

TABLE 2.—MILK EXCHANGES

Carbohydrate, 12 Gm.; Protein, 8 Gm.; Fat, 10 Gm.; Calories, 170

	MEAS.	GM.
Milk—whole	1 cup	240
Milk—skim (add two fats)	1 cup	240

TABLE 3.—VEGETABLE EXCHANGES

These vegetables may be used as desired in ordinary amounts. Carbohydrates and calories negligible.

Asparagus	Celery	Radishes
Broccoli	Cucumbers	Sauerkraut
Brussels sprouts	Eggplant	String beans, young
Cabbage	Lettuce	Tomatoes
Cauliflower	Pepper	

TABLE 4.—VEGETABLE EXCHANGES

1 serving = ½ cup = 100 Gm. Carbohydrate, 7 Gm.; Protein, 2 Gm.; Calories, 36

Beets	Peas, Green	Squash, winter
Carrots	Pumpkin	Turnip
Onions	Rutabaga	

tion of protein and fat in a serving of meat will vary with the species, the specific muscle used, and the method of cooking it. The carbohydrate in a slice of bread varies with the thickness of the slice and the type of dough used. With so many variables it was felt that the same end-result could be obtained if a system of averages was employed and the patient was careful to get variety in his diet (4).

The foods in each of the basic groups is shown in Tables 2–8. The standard diets that are available are shown in

TABLE 5.—Fruit Exchanges

Carbohydrate, 10 Gm.; Calories, 40

	Measure		Measure
Apple	1 small (2 in. diam.)	Grapefruit	½ small
Applesauce	½ cup	Grapes	12
Apricots, fresh	2 medium	Orange	1 small
Banana	½ small	Orange or other juices	½ cup
Berries: strawberries; raspberries, black	1 cup	Peach	1 medium
Cantaloupe	¼ (6 in. diam.)	Pear	1 small
Cherries	10 large	Pineapple	½ cup
Dates	2	Prunes, dried	2 medium
Figs, fresh	2 large	Raisins	2 tbsp.
		Tangerine	1 large
		Watermelon	1 cup

TABLE 6.—Bread Exchanges

Carbohydrate, 15 Gm.; Protein, 2 Gm.; Calories, 68

	Measure
Bread	1 slice
Flour	2½ tbsp.
Cereal—cooked	½ cup
Cereal—dry (flake and puffed)	¾ cup
Rice or grits, cooked	½ cup
Spaghetti, noodles, etc., cooked	½ cup
Crackers, graham (2½ in. sq.)	2
Vegetables	
Beans and peas, dried, cooked	½ cup
Corn	⅓ cup
Potatoes—white, baked, boiled	1 (2 in. diam.)
Potatoes—white mashed	½ cup
Sponge cake, plain	1 (1½ in. cube)
Ice cream (omit two fats)	½ cup

TABLE 7.—Meat Exchanges

Protein, 7 Gm.; Fat, 5 Gm.; Calories, 73

	Measure
Meat and poultry (medium fat)	1 oz.
Cold cuts (4½ in. sq., ⅛ in. thick)	1 slice
Frankfurter	1 (8–9 per lb.)
Fish: cod, mackerel, etc.	1 oz.
Cheese: cheddar, American	1 oz.
Egg	1
Peanut butter*	2 tbsp.

* Limit use of, or adjust, carbohydrate.

Table 9, and a typical menu prepared from these exchange tables is shown in Table 10. By using these tables it is possible for the diabetic patient to go to a good cafeteria, use an honest eye, and pick out the proper quantities of the foods that he is to have. Judgment of the proper quantities of the foods is aided by the illustrations in the booklet *Food Exchange Lists,* which can be obtained from the American

TABLE 8.—FAT EXCHANGES

Fat, 5 Gm.; Calories, 45

	MEASURE
Butter or margarine	1 tsp.
Bacon, crisp	1 slice
Cream, heavy, 40%	1 tbsp.
French dressing	1 tbsp.
Mayonnaise or oil	1 tsp.
Nuts	6 small

TABLE 9.—COMPOSITIONS OF STANDARD DIETS PREPARED BY JOINT COMMITTEE FROM AMERICAN DIABETIC ASSOCIATION AND THE AMERICAN DIETETIC ASSOCIATION

DIET	CARBOHYDRATE (GM.)	PROTEIN (GM.)	FAT (GM.)	CALORIES	TYPE OF PATIENT PLANNED FOR
1	125	60	50	1,200	Obese Patients
2	150	70	70	1,500	Sedentary women
3	180	80	80	1,800	Active women
4	220	90	100	2,200	Sedentary men
5	180	80	80	1,800	Children*
6	250	100	130	2,600	Sedentary adolescents*
7	370	140	165	3,500	Very active adolescents*
8	250	115	130	2,600	Active men
9	300	120	145	3,000	Very active men

*These three diets contain 1 quart; while the others contain 1 pint, of milk per day.

Diabetes Association at 1 East 45th Street, New York 17, New York. These exchange lists are self-explanatory to the point that the intelligent patient can understand them with a minimum of instruction. However, the physician should plan to spend 30–60 minutes in explaining and reviewing this material with each new patient. It is often necessary to rid the patient's mind of many of the unscientific superstitions that exist about foods before he fully understands the diet. Special diabetic foods are not necessary and are not recommended because they increase the expense of the diet

and make the patient less able to eat with other people. Diabetic ice cream which is made with skim milk and sweetened with saccharin may be used as a substitute for milk and is the one exception to the use of special foods.

In starting a patient on a diet it is important for the physician to use a positive rather than a negative approach. This is done by giving him a list of the foods that are allowed rather than a long list of prohibited foods. This is especially

TABLE 10.—A SAMPLE MEAL PLAN

(A.D.A. Meal Plan No. 2)

Carbohydrate, 150 Gm.; Protein, 70 Gm.; Fat, 70 Gm.; Calories, 1,500

Breakfast:	1 fruit exchange from Table 5 1 meat exchange from Table 7 1 bread exchange from Table 6 1 fat exchange from Table 8
Lunch:	2 meat exchanges from Table 7 2 bread exchanges from Table 6 Vegetable from Table 3 (any amount) 1 fruit exchange from Table 5 1 cup milk from Table 2 1 fat exchange from Table 8
Dinner:	3 meat exchanges from Table 7 2 bread exchanges from Table 6 Vegetable from Table 3 (any amount) 1 vegetable exchange from Table 4 1 fruit exchange from Table 5 1 fat exchange from Table 8
Bedtime:	1 cup milk from Table 2 1 bread exchange from Table 6 1 fat exchange from Table 8

important in the treatment of the hungry obese patient. The initial diet should consist of simple foods; but, as the education of the patient continues, more complicated foods can be added. Because dietary training is neglected in many medical schools, few physicians are able to readily answer all questions about foods. However, a workable knowledge of foods can be acquired from a study of the food exchange lists.

THE SULFONYLUREA DRUGS

Within recent years, tolbutamide (Orinase) (37) and chlorpropamide (Diabinese) (19) have been used in the treatment of a large number of diabetics. Carbutamide (BZ-

55) (59) and metahexamide (Euglycin, Melanex) (44) are more potent but also more toxic, and they have been discarded after intensive clinical trials. The mechanism of action of all four of these drugs is to stimulate the secretion of insulin by the intact pancreas. They may also have an action of suppressing the glucose production in the liver. All are inactive in the absence of islet cells capable of being stimulated. These drugs are ineffectual in patients with severe juvenile diabetes. In those who develop mild diabetes after the age of 40, a good initial response can be expected in about 50–75% (40); but after a period of several months the drug sometimes loses its hypoglycemic effect, and it becomes necessary to treat the patient with insulin or with phenformin (13). This delayed lack of response is termed "secondary failure" and occurs in 5–50% of the patients followed over a 3-year period. In some cases the secondary failure is due to the fact that the patient was on a low caloric diet during the first few months of treatment and would have gotten a good result from a placebo tablet during this period. After the novelty of the new tablets wore off, the patient resumed his old eating habits, resulting in a gain in weight and increased severity of his diabetes (45). In other words, some of the patients originally classified as having a good response to the sulfonylurea drugs actually had no response to the drug. A few patients develop secondary failure because of the development of intercurrent infection, such as pyelonephritis or tuberculosis. In some patients the diabetes becomes more severe, and larger doses of insulin are needed than in the past (13). The true secondary failures occur in patients who have adhered to the diet, have no infection, and have not had an increase in insulin requirements. Why these patients develop a resistance to the action of the drug is unknown, but we are not yet sure why they responded in the first place. It seems likely that secondary failure will occur in all patients if they are followed long enough (13).

There has been almost no serious toxicity from the administration of tolbutamide, and mild toxicity has been rare (37, 30). After the prolonged administration of doses of 1 Gm. or more of chlorpropamide, several cases of jaundice due to intrahepatic biliary obstruction have been reported (19). The usual maintenance dose of chlorpropamide is 250–500 mg./day, and some patients do well on as little as 100 mg./day. Under no circumstances should a dose of 1,000 mg./day be exceeded, and 750 mg./day is the usual maxi-

mum safe dose. The dose of tolbutamide is less critical. The usual maintenance dose is 500–1,500 mg./day, and a few patients may need up to 3 Gm./day in order to get the maximum therapeutic effect (45). As a general rule, there is no advantage in exceeding a dose of 2 Gm./day. Because of the fact that tolbutamide has a blood half-life of 6 hours, it is desirable to split the dose into two or three equal portions over the 24-hour period. Chlorpropamide is excreted slowly and has a half-life of 36 hours, and so it is satisfactory to give the entire dose at one time during the day (13). This is a better drug for those patients who easily forget to take medicine during the day. Because of the slow excretion chlorpropamide has a cumulative effect, and the full effects of a change in dose are not apparent until 1 week later. After cessation of the drug there are hypoglycemic effects for several days in the patient who was on tolbutamide, and for a couple of weeks in the patient who was taking chlorpropamide.

There have been statements in the literature to the effect that some patients who do not respond to tolbutamide may have a satisfactory response to chlorpropamide (19). When one uses doses that produce comparable blood levels this effect is not seen. Because of the increased potency, chlorpropamide has the advantage of costing the patient about half as much for the usual maintenance dose (13). This decreased expense and greater convenience of a single dose must be carefully weighed against the increased toxicity.

Recent reports in the literature suggest that it is possible to give tolbutamide along with insulin to severe brittle juvenile diabetic patients, reduce the insulin dose, and obtain smoother diabetic control (63). These results have not been uniformly confirmed by other investigators who tried to duplicate the procedure (13). It is likely that the brittle diabetes in some of these patients was due to the fact that they were getting an excessive dose of insulin, were having unrecognized episodes of hypoglycemia, and were overcompensating for this with secondary hyperglycemia (57). If the insulin dose is reduced in patients of this type, there is an improvement in their diabetic control (53). Once the transient hypoglycemic episodes are eliminated, the patient becomes a stable diabetic of moderate severity. This point could easily be proved by a double-blind study and the use of placebos (25). Such a study should be done by someone who thinks that there is some value in this form of treatment.

We have good evidence that long-term diabetic control with insulin is a potent factor in the prevention and delay of degenerative complications (31, 21). The time is still too short for a positive statement to be made about the sulfonylurea drugs. There has been no increased progression of the diabetic complications in the patients who have been well controlled by these drugs (15). Premature degenerative complications may occur in patients who are maintained on these drugs for several months with poor diabetic control. The maintenance of a normal blood sugar is desirable regardless of the means by which this is obtained. The physician who allows the patient to remain under poor control on oral medication when good control could readily be obtained by the use of insulin is sacrificing longevity and future health to avoid the minimal inconvenience and pain of insulin. This may make the patient happy and improve the physician's practice temporarily; but when the degenerative complications occur, this physician will regret that he did not insist on his patient's receiving the best possible treatment of diabetes.

INSULIN

Insulin is needed for all patients who cannot be well controlled by diet alone or by diet plus sulfonylurea and/or phenformin. The patient in acidosis needs insulin immediately. Patients who have had severe symptoms, ketonuria, and weight loss due to uncontrolled diabetes usually need insulin (45). The average maintenance dose of insulin in children is 0.4 units/pound of body weight (32). The initial dose in children can be 0.2 or 0.3 units/pound. In adults the average maintenance dose varies widely, but the initial dose should be about 0.1 unit/pound of optimum weight. A blood sugar evaluation should be made before the second dose of insulin is given, and the size of this dose varied according to the response obtained from the first dose. If the response is great, the dose is decreased; if it is small, the dose is increased.

The seven types of insulin currently available in the United States can be divided into three classes, depending on the speed and duration of action (see Fig. 3 and Table 11). An understanding of the similarities and differences is needed for the most efficient use of each type. Each is available in solutions containing either 40 or 80 units/cc.

Crystalline zinc insulin is the most highly purified form of

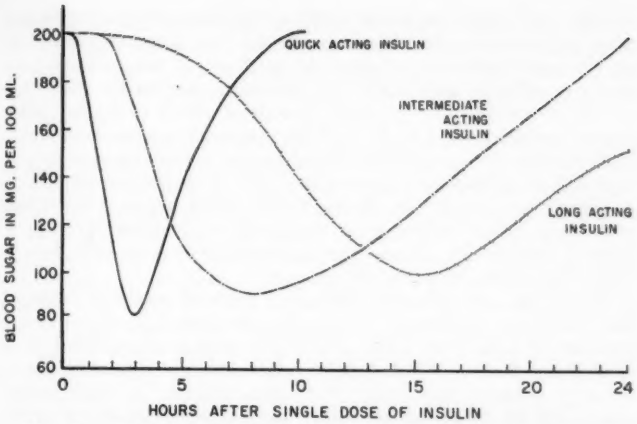

FIG. 3.—Hypoglycemic effect of the rapid, intermediate and slow-acting insulins in a diabetic person given equal small feedings (30 Gm.) of glucose every 2 hours.

TABLE 11.—TYPES OF INSULIN IN CURRENT USE CLASSIFIED ACCORDING TO SPEED AND DURATION OF ACTION

TYPE OF INSULIN	AV. ACTION TIME IN HOURS*			INTENSITY AT PEAK ACTIONS
	Onset	Peak Action	Duration	
Rapidly acting: Crystalline zinc Semilente	½	3	6	Marked
Intermediate acting: Globin zinc Isophane (NPH) Lente	2	9	24	Moderate
Long acting: Ultralente Protamine zinc (PZI)	6	18	48	Mild

*These figures are average time in hours. With smaller doses the duration of action is less than it is with larger doses.

insulin and also the most rapid in action. It is a clear solution and is the only type that should be used intravenously or for the treatment of diabetic acidosis. It starts to act 15 minutes after a subcutaneous injection, exerts its maximal effect at about 3 hours, and has little effect after 6 hours. These times are cut in half if the intravenous route is used. This insulin is sometimes added to the other types to accelerate their action (29), but the result is more predictable if a separate injection is given. When used alone, crystalline insulin is given before each meal and at bedtime in a dose that is varied with the degree of glycosuria present. In larger doses the action is more prolonged.

Protamine zinc insulin (PZI), the original modified insulin, has the most prolonged action. It contains 1.25 mg. of protamine in each 100 units of insulin and is suspended in a phosphate buffer. This insulin starts to act about 6 hours after a subcutaneous injection and reaches a peak effect about 12–24 hours later. There is still some residual effect after 48 hours. It has the disadvantage that doses that are large enough to control daytime glycosuria may cause nocturnal hypoglycemia in patients with severe diabetes. Protamine zinc insulin is useful in patients who take a dose less than 20 units each day. Many of these patients have hypoglycemic reactions just before lunch on one of the intermediate insulins but are well controlled on protamine zinc insulin. It is also useful for persons, such as truck drivers, whose occupations make it essential that they have no reactions during the day, while a mild reaction before breakfast might be tolerated. Patients taking this insulin need a small breakfast, a medium lunch, a large supper, and a bedtime feeding.

Isophane insulin (NPH) has become the most popular mixture of crystalline zinc insulin and protamine zinc insulin. It is the equivalent of mixing 3 or 4 parts of crystalline with 2 parts of protamine zinc insulin. It is suspended in a phosphate buffer and contains 0.50 mg. of protamine/100 units of insulin. It can be readily modified by the addition of more regular or protamine insulin. This insulin should be given ½–1 hour before breakfast and is useful in patients with moderate and severe diabetes. The onset of action is about 2 hours after injection, with a peak effect at 9 hours and a duration of 24 hours. In smaller doses, these times are decreased so that hypoglycemia may occur before lunch. In large doses, these times are increased so that hypoglycemia

may occur before breakfast. In moderate doses, the lowest blood sugar is in the afternoon. The usual meal plan is to give one fifth of the calories at breakfast, two fifths at lunch, and two fifths at supper. A bedtime snack is usually not necessary.

Globin zinc insulin has a similar but slightly faster action than NPH (7). The prolongation here is due to the addition of 4 mg. of beef globin to a solution of 100 units of crystalline zinc insulin. Globin insulin has the advantage that it is a clear solution but the disadvantage that the action curve from day to day is sometimes less predictable than it is with the other intermediate-acting insulins. Patients on the intermediate insulins do well on a small breakfast with an equal sized meal at lunch and supper.

In the newest modification of insulin, the action is retarded by suspending zinc insulin crystals in an acetate buffer. When small crystals are used, the product is called *semilente,* since it has an action curve intermediate between crystalline zinc and globin insulin. When large crystals are used, the product is known as *ultralente,* since it has an action curve almost as long as that of protamine zinc insulin. If 7 parts of semilente are mixed with 3 parts of ultralente, the product is known as *lente insulin;* this has an action curve that is similar to NPH but possibly is a little slower. Lente insulin has the advantage that it contains no foreign protein and, consequently, causes fewer allergic reactions. The diet distribution is similar to that for NPH. About 85% of all patients can be controlled with a single dose of this insulin given 30–60 minutes before breakfast (22). The other 15% need to have the action modified by the addition of more semi- or ultralente. Occasionally an additional smaller injection of lente is needed before supper or at bedtime.

Mixtures of regular insulin with PZI, NPH, or lente are used by some authorities, but usually the same control can be obtained by careful adjustment of the diet. In making mixtures in the syringe it is important to draw the clear insulin in before the cloudy insulin. In changing the action of lente insulin it is best to use extra parts of semi- or ultralente insulin instead of using a different type of insulin. The modification of intermediate insulin with the addition of a small amount of regular insulin is popular in Boston (29), but it is not necessary in a part of the country where the breakfast is smaller and the interval between insulin administration and eating breakfast is longer.

It is not necessary to keep the currently used bottle of insulin in the refrigerator. When the patient is traveling, it is satisfactory for him to carry the insulin in his pocket. Freezing and prolonged excessive heat, however, will result in some decrease in potency of the insulin.

The insulin needle and syringe may be kept in a dry B.D. Steritube No. 304. Since no one else is using the syringe or the insulin, it is not necessary to sterilize it each day. Boiling the syringe and steritube for 10 minutes once each week is adequate.

PHENFORMIN

In the past year, phenformin (phenethyldiguamide, DBI) has been released for the treatment of diabetes (65). This drug is effective in lowering the blood sugar in about two thirds of the patients with diabetes. At present there are no criteria by which one can predict effectiveness before the drug is tried. It will lower the blood sugar in some of the patients with mild cases that do not respond to tolbutamide or chlorpropamide, or in patients who previously responded to these drugs but who are now secondary failures (34). There is another group of patients who can be adequately controlled on a combination of phenformin and sulfonylurea but who do not obtain a satisfactory response on either drug alone; in this group it is usually easier and less expensive to use insulin, but if a patient has once been treated with oral medication it is difficult to persuade him to return to insulin. The most promising group for phenformin is the severe juvenile diabetic who has wide fluctuations between hyperglycemia and hypoglycemia (35). In these patients it is sometimes possible to reduce the insulin dose, add phenformin, and obtain a much smoother course of diabetic control. Sometimes the beneficial results in this group are the result of reducing a previously excessive insulin dosage; at other times the benefit is due to the fact that the patient is being checked much more closely, and, consequently, he is being more careful about his diet. Before success can safely be attributed to this drug, it is necessary for the physician to substitute a placebo without the patient knowing of the change. The physician and the patient will be amazed to find how often the placebo is equally as effective.

Phenformin has no known toxic effects, but its side effects often limit the amount of medication that can be given. If

a large enough dose is given, all patients will get severe nausea and vomiting, which will subside after the drug has been withheld for several days. During this iatrogenic illness the patient may need intravenous glucose infusions and extra doses of insulin. This complication can sometimes be handled in the home or in the well-equipped office, but when severe, it calls for hospitalization. Patients who have been made sick by this drug are reluctant to try it again; and if the sickness required the added expense of hospitalization, they are even less enthusiastic about the drug. It is therefore important to watch closely for the first symptoms of overdosage and to reduce the dose when these appear. The symptoms may occur on a dose that has been satisfactory for several weeks. The dose must be increased very slowly and should be sharply reduced at the first sign of metallic taste, anorexia, or nausea.

Because of the anorexic effects of the phenformin in large doses, it was thought that the drug might be beneficial in the obese patient. A drug that would lower the blood sugar at the same time that it decreased the appetite would seem to be the answer to the difficult problem of the fat diabetic. We tried phenformin in 12 such patients in the diabetic clinic at Georgetown Hospital with uniformly poor results (61). The margin between the anorexic dose and the vomiting dose was so narrow that the patients who had a beneficial effect usually quit the drug in disgust and resumed insulin.

Because the duration of action of phenformin is 5–6 hours, it is necessary to give the drug in divided doses. The usual starting dose is one 25 mg. tablet at breakfast and supper. If the response is inadequate and there are no side effects, the dose is increased after several days to one tablet with each meal and later to another one at bedtime. This is the average dose that our patients have been able to tolerate; but some have taken twice, and very rarely, three times this dose. In general, there should be at least 1 week between each increase in dose.

In patients with the maturity-onset type of diabetes who are not taking insulin, the dose of phenformin is increased slowly until the criteria of control are satisfied or side effects appear. In patients with severe unstable juvenile diabetes, the insulin must be continued but the dose gradually reduced as more effect is obtained from the phenformin. This is a difficult and unpredictable process. If the insulin is not reduced enough, severe hypoglycemia may occur; but if it is

reduced too much, marked ketonuria may occur. One of the striking effects of phenformin is the presence of a large amount of acetone in the urine in the absence of any sugar. This almost never occurs in the patient who is taking insulin alone, and makes it essential that the patient test for acetone as well as for sugar at least four times each day. When there is acetonuria but no glycosuria, it is necessary to give the patient extra carbohydrate immediately. The next day the dose of insulin is increased and the dose of phenformin decreased. In order for this drug to be used safely, the physician must be within reach by telephone 24 hours each day for the first few weeks. Hospitalization during the period of initial control is prolonged and costly but may be desirable when the patient lives a great distance. Under these circumstances it would probably be better for the patient to get a physician who lives closer to manage the treatment.

Long-acting capsules of 100 mg. of DBI have been prepared and are in the stage of clinical trial. These have the advantage that the entire dose can be given at breakfast. In this form some patients are able to tolerate larger doses than they could with the tablets. However, the capsules have the disadvantage of less flexibility of dose (61). In some patients the capsules and the tablets are used simultaneously with good results.

CLASSIFICATION OF PATIENTS

As has been alluded to earlier in this paper, the treatment that is effective for one patient is not necessarily effective for another (61, 55). This does not mean that diabetes represents more than one disease. It does mean that the reaction to insulin deficiency is variable depending on the age of the patient, the amount of obesity, the condition of the liver, and the degree of damage to the pancreas. The same hereditary trait can be found in those patients who are thin and have a total absence of insulin in the pancreas as in those who are fat and have a normal amount of insulin in the pancreas (29). With the possible exception of the rare patient with hemochromatosis, all diabetics eventually develop the same degenerative complications. It is usually possible to predict the most effective treatment at the time of the first visit of the patient (Fig. 4), but in borderline patients it is often necessary to change the method of treatment later.

Prediabetes

Years before the onset of clinical diabetes, evidence that the patient may eventually develop diabetes is often present (46, 3). People with a positive family history of diabetes are five times as likely to develop the disease as are those with a negative family history (29). The child who is excessively tall and the adult who is overweight are more likely to develop

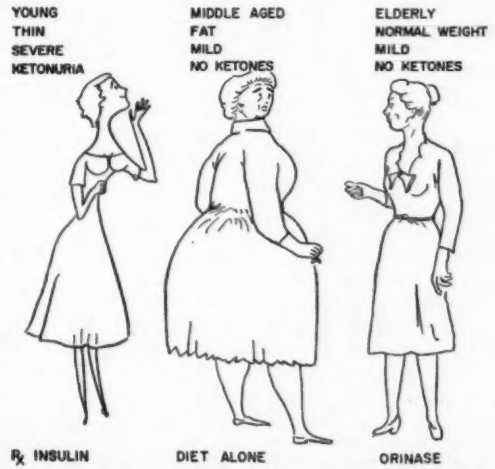

Fig. 4.—The initial treatment of the patient with diabetes can be decided after he is classified into one of these three main groups. If the initial results are poor, the therapy is changed and intensified.

diabetes than are those who are small and thin. Babies who are larger than 10 pounds at birth are more likely to develop diabetes in later life. The increased incidence of diabetes in women is related to the number of pregnancies; and in women who have never been pregnant, the incidence of diabetes is the same as it is in men. As pointed out by Kriss and Futcher (36) and confirmed by others (46, 51), pregnancies in women who later develop diabetes are often abnormal and have the same abnormalities that are seen in diabetic women. From a statistical standpoint, the most striking abnormality is the birth weight of the baby. If the baby

is over 10 pounds, 18% of the mothers will develop clinical diabetes. If the baby is over 11 pounds, the figure is 25%; if over 12 pounds, it is 51%; and if over 13 pounds, it is 63% (36). Glucose tolerance tests done shortly after delivery on women who have given birth to babies over 10 pounds show that one third of them have persistent hyperglycemia even though the fasting blood sugar is normal (41).

Spontaneous hypoglycemia is often a precursor of diabetes, as shown by Seltzer, Fajans, and Conn (56). These patients may have a normal glucose tolerance test for the first 3 hours, but then they develop hypoglycemia with the usual symptoms. Over a period of years many of these patients learn to eat something at the onset of these symptoms, and they think that there is nothing abnormal in their need for a "coffee-break" midmorning, midafternoon, and at bedtime. Unless they curtail their food intake at the other meals, they may become excessively obese. These patients account for a small group of obese patients who get weak, nervous, irritable, dizzy, and sometimes actually sick when they try to lose weight. However, they can lose weight with a low calorie, high protein, six-meal diet and a lot of will power.

The prediabetic state should be suspected when there is one or more of these factors. The diagnosis can be confirmed by finding a minor abnormality in the glucose tolerance curve. When this test is normal, it can be made more sensitive by repeating the test after the patient has been primed with cortisone (16). This will yield a diabetic tolerance curve in the prediabetic patient but not in the normal patient. The actual predictive value of this test will not be known until patients taking the test have been followed for many years. At present it does seem to be a means of detecting diabetes in the preclinical stage, before any complications have developed, and at a time when preventive treatment may be instituted.

The one preventive measure that all can agree on is the avoidance of obesity. It makes good sense for everyone to avoid obesity, but it is imperative in one who has been demonstrated to be a prediabetic patient. In these people the physician has strong arguments that he can use. He should have the patient return several times each year for a blood sugar test and a check on the weight. Reducing the weight to less than the so-called optimal weight will certainly delay the onset of clinical diabetes and may prevent it entirely (8).

The long-term treatment of these patients with small doses

of tolbutamide has been advocated on the theory that this might cause hyperplasia of the beta cells of the islets of Langerhans (16). Even though tolbutamide is one of the safest drugs in use today, its use probably is not justified on the basis of the available evidence. The possibility that the long-term use of tolbutamide would result in earlier exhaustion of the islets is an important consideration that needs further study. Tolbutamide almost never causes significant hypoglycemia in the person with diabetes, but it may cause hypoglycemia in the nondiabetic and serious hypoglycemia in patients with hyperinsulinism (45). This fact would make its use hazardous in prediabetic patients.

The administration of small doses of insulin to these prediabetic patients has been recommended on the theory that the pancreas needs an opportunity to rest and recuperate. The use of insulin during pregnancy in these women has been suggested by Hoet (24) as a method for decreasing the complications of pregnancy. This has been confirmed by others, but more study is needed. Insulin probably should never be started in any patient with normal fasting blood sugar. After insulin has once been started, the second physician who sees the patient is always reluctant to stop it.

The prediabetic patient should be searched for, carefully evaluated, and warned that he is a potential diabetic. He should test his urine and obtain a blood sugar test at least twice each year and at any time that he is sick with any acute illness. These borderline patients should not be given a definite diagnosis of diabetes because that would automatically increase their insurance premiums and close the door to many new job opportunities. They should tell each new physician that they see that they are potential diabetics so that he can be alert to symptoms that might indicate clinical diabetes.

The Obese Diabetic

Patients who are grossly overweight are a much more common sight in large diabetic clinics than they are in private practice, but they are entirely too common in both places and are a source of constant frustration to the physician. The possibility that the underlying disease may be Cushing's disease, pheochromocytoma, or islet cell adenoma must be kept in mind in these patients. A search for such exotic diseases usually ends up with a diagnosis of exogenous

obesity. The theoretical treatment of these patients is simply a matter of telling them to eat less, but in practice it is much more difficult. Those who actually do reduce their caloric intake are rewarded by a subsidence of their diabetic symptoms, the cessation of glycosuria, a normal fasting blood sugar, and eventually, the postprandial blood sugar may return to normal. When the symptoms are severe or when there is marked acetonuria, insulin should be used. Even though the diabetes is mild, a large dose of insulin is needed to give these obese patients a normal blood sugar if they continue to eat excessively. Many have a lower blood sugar while in the hospital on a measured 1,200-caloric diet and no insulin than they have at home on 80 units of insulin and their usual unrestricted diet.

The results with tolbutamide are equally disappointing in the grossly obese patients. When placebo tablets were given to a group of six fat clinic patients, they lost weight and had a nice fall in their blood sugar level. After the novelty of the new pills had worn off, the weight loss stopped and the blood sugar started to rise. At this point these patients were started on tolbutamide, but they did not know that they were getting different pills. Their weight gain continued and their blood sugar leveled off at around 180 mg./100 ml. (45). If the tolbutamide had been given first, these patients would have been classified as having had a good initial response with the development of secondary failure after several weeks of treatment. This phenomenon accounts for many of the secondary failures to tolbutamide that have been reported (13). Sometimes the response to tolbutamide is good for a long period of time despite continued obesity. In these patients the physician may feel that he is doing some good, but the results are never so good as could be obtained by rigid adherence to caloric restriction.

Many appetite-depressant drugs have been tried with temporary improvement but with no long-term success. Most of the glowing reports in the literature are short-term experiments and do not extend over the many years that patients have diabetes. Most patients who lose weight by taking drugs regain this weight (and often more) after cessation of the medication. The only solution is to teach the patient proper eating habits which he can use for the rest of his life and to try to give him sufficient motivation to continue these eating habits after the initial novelty has worn off and he has grown tired of "punishing" himself. This can be accomplished only by an intensive educational program designed

to show the harmful effects of obesity, the benefits of weight reduction, and a simple explanation of how this can be accomplished.

The Elderly Diabetic of Normal Weight

In this group of patients the sulfonylurea drugs are most successful (13). These patients usually have few symptoms. Their diabetes is often discovered when glycosuria is found in a routine urinalysis done as part of a physical examination. Some of these have degenerative complications at the time the diabetes is diagnosed, making it evident that they have had diabetes for several years. Simple caloric restriction has little to offer these patients who are already near normal weight. Insulin is effective, but its administration is often difficult because of poor eyesight, unsteady hands, and stiff joints. The sulfonylurea drugs are less effective in patients who have had a marked weight loss due to uncontrolled diabetes. They are often very effective in those patients who were obese, lost weight by dieting, and still have uncontrolled diabetes.

The usual maintenance dose of tolbutamide is 1–1½ Gm./day. Sometimes 2, and rarely 3, Gm. are required for good control (45). A few patients do well on ½ Gm./day and, rarely, on ¼ Gm. It is customary to give a loading dose of 3 Gm. the first day and 2 Gm. the second day. Then the patient is followed daily. If the patient is seen at weekly intervals, it may be better to start on one tablet with each meal (1½ Gm./day). Dividing the dose into two or three equal parts often improves the degree of control. Because of the possibility of the insidious development of secondary failure, it is wise to see these patients at least every 2 months.

It is often possible for patients who are well controlled on tolbutamide to go through major surgery, pregnancy, gangrene, and even pneumonia without additional insulin. However, since all of these stresses do have a tendency to aggravate the diabetes and increase the insulin requirements, it is necessary to follow these patients closely and give supplemental injections of insulin, as needed, to help the patient through the critical stage. No longer can it be said that surgery or infection is an absolute contraindication to the use of tolbutamide (45).

Chlorpropamide is more potent, more toxic, and more economical than tolbutamide. The entire daily dose can be given at one time, and it takes 1 week to determine the full

effect of a change in dosage. Some patients may get a good response to this drug after failing to get a good response to tolbutamide. The average maintenance dose is 250–500 mg. (13).

If adequate diabetic control is not obtained after the patient has taken the maximum dose of tolbutamide or chlorpropamide for a couple of weeks, some other form of treatment must be considered. If there has been some response to the sulfonylurea drug, the addition of DBI may result in good control. If there has been no demonstrable effect from the sulfonylurea drug, it may as well be discontinued before starting DBI. If the patient has had ketonuria, weight loss, or other severe diabetic symptoms, insulin should be started. When a poor response is obtained with an adequate dose of tolbutamide (3 Gm./day), it is unlikely that a better response will be obtained with the maximum safe dose of chlorpropamide (0.75 Gm./day). However, exceptions do occur in perhaps one fifth of the patients.

The Thin Ketotic Juvenile Diabetic

Patients who have severe symptoms at the onset of diabetes, who have lost weight because of uncontrolled diabetes, who have ketonuria, and who are less than middle aged at the time of onset usually require insulin (45). In these patients the sooner the insulin is started the better. It often helps for the physician to give a small injection and have the patient then give himself a similar injection of insulin as soon as the diagnosis of diabetes has been confirmed by the report of a substantial blood sugar evaluation. Trying these patients on diet or oral medication first is a waste of time and makes it much more difficult to get them started on insulin later. These patients will show temporary symptomatic improvement after restriction of carbohydrate, but this slight improvement is hardly worth the effort. There may be less glycosuria after the administration of large doses of tolbutamide, but the blood sugar almost never falls to normal and there is no return of weight and strength.

Some slight response is evident if the sulfonylurea drug is given at the onset of acute diabetes, and more response is noted if the drug is given at the onset of the usual remission that these young people have. However, the continued administration inevitably leads to constant hyperglycemia, hyperlipemia, weight loss, and the rapid development of diabetic neuropathy or other degenerative complications. Some

of these patients may have ketonuria for many months before a mild infection precipitates an episode of diabetic coma. After the patient has been told that insulin is necessary, he may look for a new physician in the hope of obtaining a different opinion. It is best never to hold out the hope of oral medication in these patients.

Patients who are not in acidosis can usually be regulated in a satisfactory manner in the office. The initial dose of either lente or NPH insulin should be about 0.1 units/pound of body weight in patients with moderate symptoms and 0.2 units in those with severe symptoms or marked ketonuria. The next morning it is desirable to have the patient return for a fasting blood sugar. At this time the physician can watch him give the second injection of insulin to himself and correct his technic of administration. Usually the same size dose will be given the second day. If there has been a marked fall in the blood sugar, this dose may be reduced; if there has been no change, the dose may be increased. Much time must be spent in the education of the new patient; it cannot all be done at one visit. At the first visit an explanation of what diabetes is and how to give the insulin injection is sufficient. The patient is permitted to eat his usual meals this day. At the second visit the injection technic is reviewed, the patient is shown how to test urine for sugar and acetone, and the diet is explained to him. The next morning the patient phones in a report of his symptoms and the results of his urine tests. Some minor adjustment of the insulin dosage may be needed at this time. The next day he comes in for a blood sugar test, a review of the urine tests, and a check on the symptoms and the weight. At this time the diet is reviewed and his questions about diet are answered. This visit could be before breakfast if it is felt that more supervision of the injection is needed, or it could be before lunch or late in the afternoon if it is felt that the blood sugar may be too low at one of these times. Later visits are spaced farther apart, but a daily phone report is insisted on during the first week or two. The time of the visits is varied so that the high and low points of the blood sugar curve can be recognized. If there is the pattern of a high blood sugar at one time of the day and a low blood sugar at another, it is a simple matter to move food from one meal to another. If the initial diet was low in calories, food can be added at the time of the day when it is most needed to raise the blood sugar.

Patients who are in early diabetic acidosis should be admitted to the hospital for the initial regulation. These pa-

tients can be started on a dose of lente insulin equal to 0.2 units/pound plus regular insulin before each meal, depending upon the amount of sugar in the urine. The widely used rule of 5 units of regular insulin for each plus of the urine sugar sometimes results in too much insulin. A safer rule would be to ignore a 1+, but give 4 units for 2+, 8 units for 3+, 12 units for 4+, and an extra 4 or 8 units for moderate or marked acetonuria. Every second day the total amount of regular insulin given should be added and the daily dose of intermediate insulin increased by half this amount. Because the full effect of a change in the dose of intermediate insulin is not seen for more than 48 hours, the dose usually should not be raised more often than every other day. A fasting blood sugar test should be done at least every other day during the initial hospital regulation. As soon as negative urine tests are obtained, it is necessary to check the blood sugar at that time of the day in order to avoid hypoglycemia. While in the hospital, the patient should give his own injections and test his own urine as soon as he is physically able. The dietician should see him on the second hospital day and again immediately before discharge. Much good teaching time is lost if the dietician is only asked to see him on the morning of discharge. If the hospital has a podiatrist in attendance, it is often desirable for him to see the patient before discharge. This is especially important in elderly people with arteriosclerosis and neuropathy.

The usual maintenance dose of insulin in children is close to 0.4 units/pound of body weight (32), and in children with severe symptoms it is safe to start with this dose in the hospital. If the patient is closely regulated at the time of discharge, it may be necessary to reduce the dose of insulin about 5 units in order to avoid an insulin reaction as soon as he returns home and resumes more exercise. This reduction is especially important in children, but the amount of the decrease is less in the younger ones. Another phenomenon that must be kept in mind in the treatment of children and young adults is that initial regulation is often followed by a marked reduction in the severity of the diabetes. The insulin requirement may drop to as little as 0.1 unit/pound a few weeks after discharge. Some children may get along with no insulin for a few weeks. Since this remission is always temporary, it is usually best to continue to give the patient a small dose of insulin each day and to warn the parents not to become overly optimistic because of the reduction in the

insulin dose. As the child grows older, it is necessary to increase the insulin dose.

Much time must be spent in the proper education of the child and his parents. The diet and insulin administration must be adjusted to his school schedule. A large snack after 3 p.m. is desirable. Sometimes a small snack at 11 a.m. is necessary in order to prevent hypoglycemia before lunch. It is usually possible for the child to eat some crackers or fruit at this time without calling too much attention to himself. If the late morning snack is impractical, the addition of an extra meat and fat exchange to the breakfast may solve the problem. The diabetic child should take part in all of the extracurricular activities in which the other children take part. They must learn to eat extra for competitive sports and not to withdraw from competition because of diabetes. They need to go to birthday parties and dances, as do the other children. By omitting a bread, fat, and milk exchange at supper, the child is usually able to eat a small serving of ice cream and cake without significant effect on his diabetes. The teen-age child soon learns that a couple of hours of strenuous dancing is the equivalent of a "coke" and a couple of cookies at intermission. By omitting his usual bedtime snack he may even be able to eat a hamburger at one of the drive-in shops on the way home. By making these concessions as a positive action early in the course of treatment, the child is less rebellious than when these are denied him and he is made to feel "different."

SUMMARY

Disability from diabetes mellitus is prevented by early diagnosis and careful control of the disease. The patient who is well controlled has no diabetic symptoms, no hypoglycemic episodes, maintains an optimum weight, has a blood sugar near normal before each meal, and has little or no sugar in the urine.

All diabetic patients need some type of dietary guidance. This can most easily be accomplished with the use of the food exchange lists of the American Diabetic Association. The diet needs to be tailored to the habits of the patient and the resultant blood sugar curve.

At the time of the original diagnosis, the patients can be classified into: the mild obese diabetics who can be controlled by caloric restriction; the older nonobese, nonketotic diabetics who can be controlled by tolbutamide or chlorpropamide;

and the thin, ketotic, or young diabetics who need insulin.

Phenformin is useful in increasing the efficiency of insulin and the sulfonylurea drugs. It is also effective in some of the older patients who do not respond to the sulfonylureas alone. At the present time, there are no clear criteria for the use of this drug in a new patient, but it is a valuable adjunct to the treatment of patients who are not doing well on their present regimen.

With careful attention to the details of diet and hypoglycemic medication, a patient with diabetes should be able to live a normal, a useful, and a long life.

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